PRION DISEASES

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Prion diseases or transmissible spongiform encephalopathies (table 1) are characterised by the deposition of PrP^{Sc}, an abnormal form of a normal cellular protein, PrP^{C}. These diseases exist in sporadic (idiopathic), genetic, and acquired forms.

PRION PROTEIN

The normal prion protein, PrP^{C}, is encoded by the prion gene (*PRNP*) on human chromosome 20, with equivalent prion genes in animals. The function of PrP^{C} is not known but it may have roles in anti-oxidant systems and cellular copper metabolism. In prion diseases, the normal host gene produces the normal host PrP^{C} but there is then an incompletely understood post-translational conformational change to a disease related form, PrP^{Sc}. PrP^{Sc} is relatively insoluble and relatively protease resistant, and accumulates in tissues forming amyloid structures. The precise pathogenesis of the neurological illness is not known, but PrP^{Sc} deposition is associated with the neuropathological changes of neuronal loss, astrocytic gliosis, and spongiform change (fig 1). In the acquired prion diseases, material from an affected host infects another. The infective agent (termed the ''prion'') has not been fully characterised, but PrP^{Sc} is associated with infectivity.

Since the prion protein has such a central role, it is not surprising to find that the prion protein gene, *PRNP*, is also important (even in non-genetic forms of TSE). In human prion diseases, a common polymorphism at codon 129 has important effects on susceptibility to disease, the resulting clinical characteristics and the incubation period (in acquired forms). At codon 129 of *PRNP*, an individual may encode for methionine (M) or valine (V) and, therefore, all humans are MM or VV homozygotes or MV heterozygotes. In the normal UK population, the distributions are approximately: MM 40%, VV 10%, MV 50%. Some effects of this polymorphism are discussed in specific sections below. Two basic facts illustrate the potential importance of this polymorphism: approximately 80% of UK sporadic CJD cases and, to date, all cases of variant CJD, are MM (table 2).

This review is concerned with those human prion diseases of relevance to clinical neurological practice in the UK: Creutzfeld-Jakob disease (CJD), Gerstmann-Sträussler-Scheinker syndrome (GSS), and fatal familial insomnia (FFI). These diseases are very rare but, nonetheless, are of importance and interest.

SPORADIC CJD

What is sporadic CJD?

Most cases of CJD occur on a sporadic, worldwide basis without any currently recognised genetic, iatrogenic or other cause, affecting approximately one person per million per year. Sporadic CJD (sCJD) is generally regarded as a spontaneous neurodegenerative illness, arising from either a spontaneous PRNP gene somatic mutation or a stochastic PrP protein structural change. In either case, one would expect a continuously increasing incidence with increasing age, yet, characteristically, sCJD has a peak incidence in the seventh decade, with a decline in the very elderly (fig 2). In recent epidemiological studies, including in the UK, there has been an increase in the incidence in the elderly, and there may have been under-ascertainment of cases in this age group. sCJD could be an acquired illness despite failures to identify a definite external cause; two recent case–control studies (in Australia and the UK) have found a relative excess of previous surgery in the cases. Naturally, sCJD may not be aetiologically homogenous, with possibly some cases being spontaneous and others possibly being iatrogenic. To date, there is no evidence to support a dietary cause.

As stated above, being codon 129 MM is clearly a risk factor for sporadic CJD, with MV heterozygosity affording a partial protection (80% of cases and 40% of normal UK population being MM; 10% of cases and 50% of the normal UK population being MV) (table 2).

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Table 1 Prion diseases

Animal diseases	Notes	Human diseases	Notes
▶ Scrapie	Naturally occurring disease of sheep and goats	▶ Kuru	Confined to Papua New Guinea Related to cannibalistic mourning rituals
▶ TME	Transmissible mink encephalopathy, a disease of farmed mink	▶ CJD	The most common human prion disease. First described in 1921 Exists in four forms: Sporadic Genetic Iatrogenic Variant (described 1996)
▶ CWD	Chronic wasting disease of deer, confined to North America	▶ GSS	Gerstmann-Sträussler-Scheinker syndrome, a rare autosomal dominant hereditary disease
▶ BSE	Bovine spongiform encephalopathy, disease of cattle first reported 1987	▶ FFI	Fatal familial insomnia, a rare autosomal dominant hereditary disease
▶ BSE related diseases	Transmission of BSE to cats (FSE) and other animals		

What is sporadic CJD like?

sCJD typically presents with a rapidly progressive dementia. Other neurological features appear including cerebellar ataxia and, most characteristically, myoclonus. The speed of progression often alarms relatives or friends and may surprise the clinician; initial investigation plans may well be overtaken by clinical developments. In some cases, the onset is so abrupt as to suggest a stroke, although the subsequent progressive course will cause the clinician to reconsider. The ability to walk and speak is often lost early. In a typical case, the progression culminates in a terminal akinetic mute state with myoclonus.

There is clinical heterogeneity in sCJD, especially at the onset when particular focal deficits may be present. Highly atypical clinical profiles have been reported but such cases are relatively rare instances of an already very rare disease. However, clinical neurologists should be at least aware of two specific variations:

- firstly, presentation with an isolated, progressive cerebellar syndrome over several weeks, or occasionally longer, before the appearance of other features including dementia
- secondly, presentation with isolated, progressive visual disturbance culminating in cortical blindness.

The basis for this clinical heterogeneity (which is paralleled to some degree by variations in the neuropathology) is not entirely understood and a detailed discussion is outwith the remit of this review. However, it does, in part, reflect different codon 129 genotypes, or the type of prion protein deposited in the brain.

The median duration of illness in sCJD is four months, with around two thirds dying within six months. Fourteen per cent of cases have illness durations of a year or more, and only 5% of two years or more (fig 3). As a general guide, if an individual is still able to walk and talk at a year, then sCJD is unlikely.

How do I diagnose sCJD?

The diagnosis should be considered in any individual presenting with a rapidly progressive dementia (characteristically developing over weeks) when other more common causes have been excluded. The early presence of other neurological features (especially cerebellar or visual) is helpful, and the development of myoclonus is characteristic (although not invariable and, of course, not unique to CJD). A general outline of the diagnostic process is given in table 3.

Table 2 PrP codon 129 genotype distributions

	MM (%)	MV (%)	VV (%)
Normal population	39	50	11
sCJD (UK 1990–2002)	68	16	16
vCJD	100	0	0

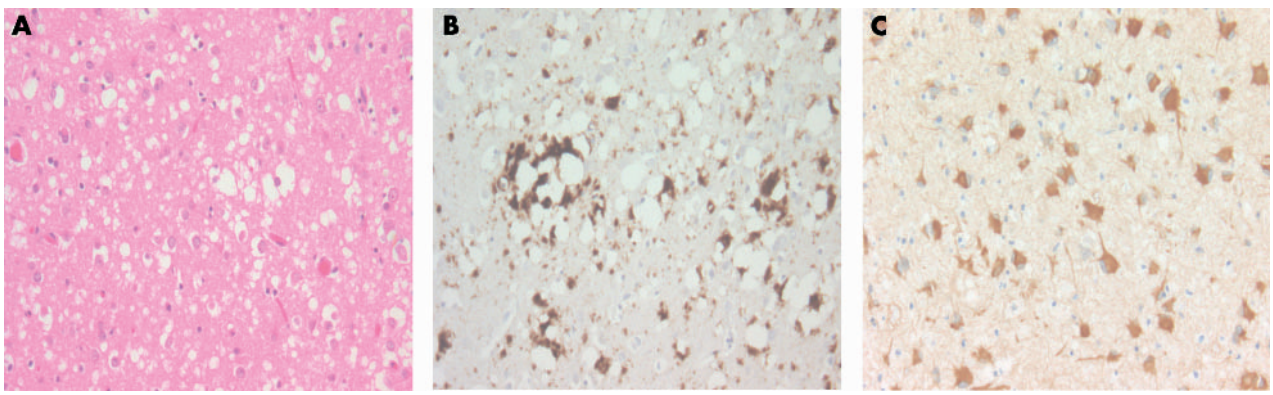

Figure 1 Neuropathological changes in Creutzfeld-Jakob disease (CJD). (A) sCJD: spongiform change in the frontal cortex (haematoxylin and eosin). (B) sCJD: cerebral PrP deposition (KG9 antibody). (C) vCJD: thalamus showing gliotic change (glial fibrillary acidic protein antibody). Courtesy of James Ironside and Linda McCardle, National CJD Surveillance Unit.

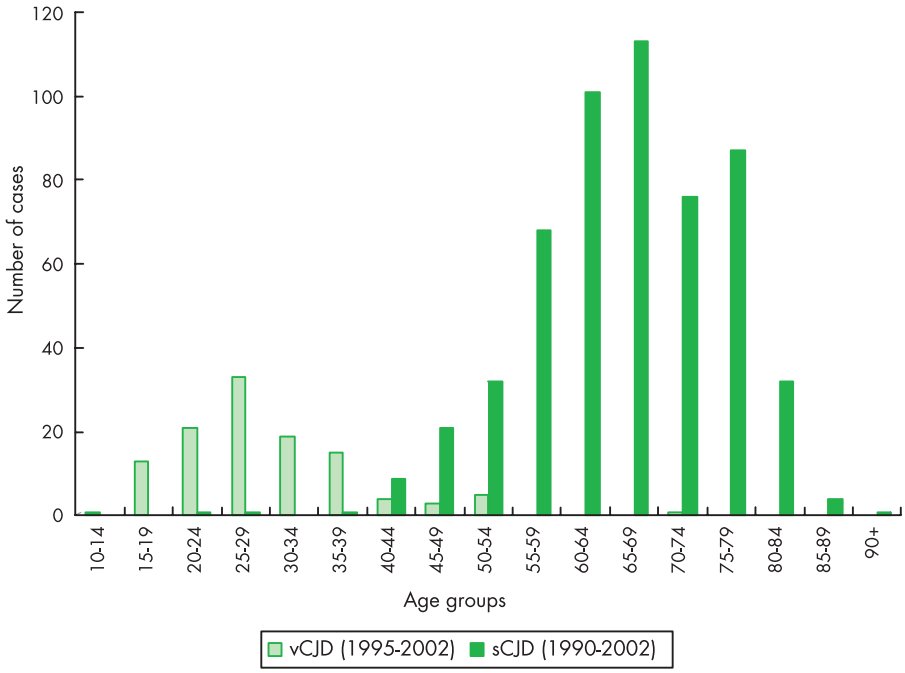

Figure 2 Age at death of variant and sporadic CJD in the UK by five year age groups.

It is critical to exclude other possible diagnoses. Quite aside from non-CJD illnesses, it is important to consider genetic, iatrogenic, and variant forms of CJD. This requires consideration of the clinical profile, a detailed past medical history (to cover potential iatrogenic causes), a careful family history, genetic testing, and the use of investigations. There are three investigations of particular diagnostic utility: the electroencephalogram (EEG), cerebrospinal fluid (CSF) 14-3-3, and magnetic resonance imaging (MRI).

A definite diagnosis requires neuropathology, but a high degree of clinical confidence can be achieved in most cases. There are published clinical diagnostic criteria (also available on www.cjd.ed.ac.uk) and any case classified as ''probable'', according to these criteria, has around a 95% likelihood of having sporadic CJD. This requires a correct understanding of the criteria and a careful clinical assessment, but it represents a greater degree of certainty that is attached to the use of the term ''probable'' in the clinical diagnosis of many other neurological conditions!

Cerebral biopsy can, of course, provide neuropathological confirmation in life. However, it should be considered only if there is a reasonable possibility of it confirming an alternative, potentially treatable disease, and it is only rarely necessary.

Table 3 Diagnosis of sporadic CJD

► Awareness of sCJD	
► A rapidly progressive dementia	
► Other early neurological features (especially cerebellar or visual)	
► Myoclonus	
► Exclusion of other diagnoses (including other forms of CJD)	
► MRI	Exclusion of other diagnoses Findings suggestive of sCJD
► EEG	Periodic discharges
► CSF	Exclusion of other diagnoses (e.g. no pleocytosis) Positive 14-3-3

EEG

The EEG shows a progressive deterioration in the normal background rhythms and, in around two thirds of cases, the appearance of periodic sharp wave complexes (PSWCs) (fig 4). These important points should be noted:

- The absence of PSWCs does not exclude the diagnosis
- PSWCs may be present in other conditions (for example, hepatic encephalopathy, drug toxicity and, rarely, Alzheimer's disease)
- If PSWCs are absent on an initial EEG, repeat EEGs may show their development (repeat testing should be considered at around weekly intervals)

CSF 14-3-3

CSF 14-3-3 is a normal neuronal protein that has no specific connection to CJD, being released into the CSF following neuronal damage. It is, therefore, perhaps surprising that it has specific diagnostic utility in CJD. However, many of the conditions that cause elevated CSF14-3-3 concentrations can be reasonably readily differentiated from sporadic CJD on clinical grounds. A positive 14-3-3 test may therefore strongly support a clinical diagnosis of sCJD, but the reported specificity and sensitivity (both around 94%) are valid only in an appropriate clinical context. CSF 14-3-3 is useful in cases where sCJD is a sensible possibility and other possibilities have already been excluded by reasonable neurological assessment and investigation.

The CSF will almost certainly be examined in any case in the exclusion of other diagnoses: the 14-3-3 test does not usually require a separate investigation, providing CSF has been stored. There is a national 14-3-3 laboratory service run by the National CJD Surveillance Unit (NCJDSU) in Edinburgh (contact details below).

MRI

Cerebral imaging is a vital part of the exclusion of other diagnoses, and normal brain imaging, in the face of a rapidly progressive, devastating encephalopathy, may lead to a consideration of sCJD. However, in some cases, the MRI

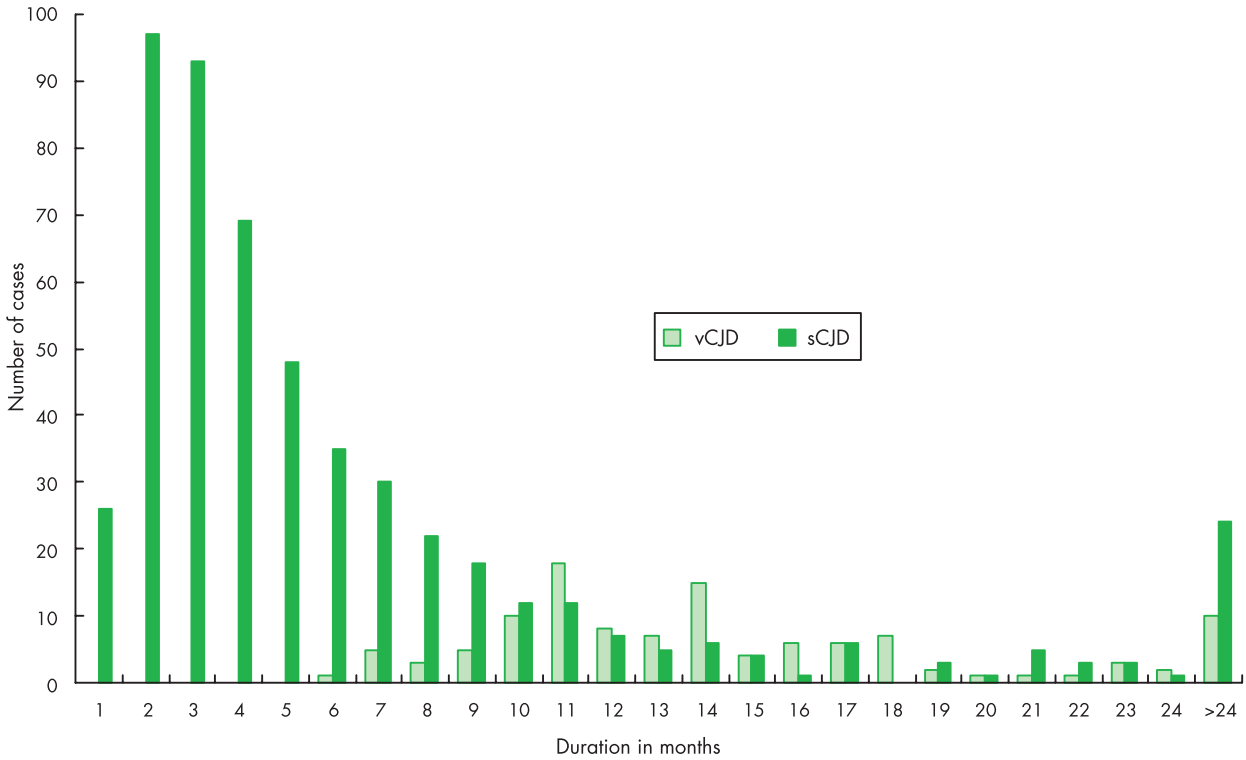

Figure 3 Duration of illness (months) in variant and sporadic CJD.

shows a characteristic signal change in the putamen and caudate (fig 5). Occasionally, high signal may be seen in the cerebral cortex, generally focal and reflecting the particular clinical features at the time of imaging. Significant atrophy is unusual if imaging is undertaken within three months of disease onset.

GENETIC PRION DISEASES

What are genetic prion diseases?

The basic definition of genetic prion disease is simple: disease related to an underlying mutation of the prion protein gene (*PRNP*) on human chromosome 20. However, there are a significant number of recognised mutations and a wide variety of clinical illness phenotypes. The resulting complexity is increased by the use of disease labels (partly eponymous) that have probably outlived their practical utility (table 4). The underlying abnormalities are point mutations (such as E200K) and insertions (such as ins24bp). The latter occur in a region of the gene that encodes for a functionally important octapeptide repeat part of PrP. Insertions in this region lead to expansions of the octapeptide repeat number and the size of the insertion affects the clinical phenotype (as in Huntington's disease).

In general, other genetic factors (particularly the codon 129 polymorphism) may influence the clinical phenotype (including age of onset and illness duration) resulting from a given mutation. Most notably, the D178N mutation gives rise to the clinical picture of genetic CJD when associated with 129-V on the mutant allele and yet results in FFI when associated with 129-M. This fact illustrates how the classical nomenclature of genetic prion diseases should perhaps be abandoned in the light of modern molecular understanding.

Overall, the most common mutation is E220K. There are important particular foci of genetic prion disease, most particularly in Israel, Slovakia, and Chile. In the UK, there are only a few deaths per year from genetic prion disease.

Table 4 Genetic prion diseases and mutations

Genetic prion diseases
Genetic CJD
FFI
GSS
Associated *PRNP* mutations
E200K, V180I, T183A, H208R, P102L, D178N, M232R, V210I, F198S, 145stop, A117V, Q217R, Q212P
Ins24bp, ins48bp, ins96bp, ins120bp, Ins144bp, ins168bp, ins216bp, ins192bp

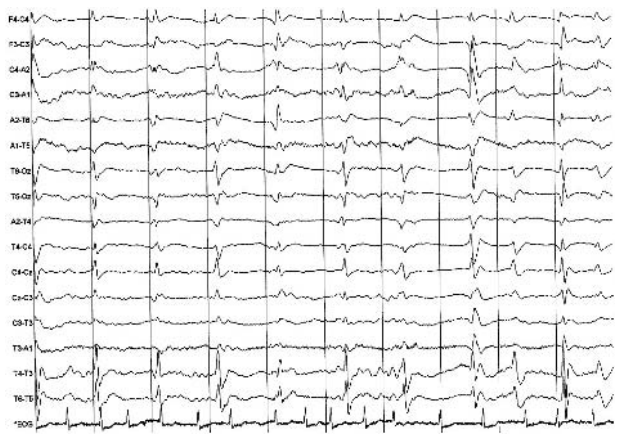

Figure 4 The typical periodic EEG seen in many cases of sporadic CJD.

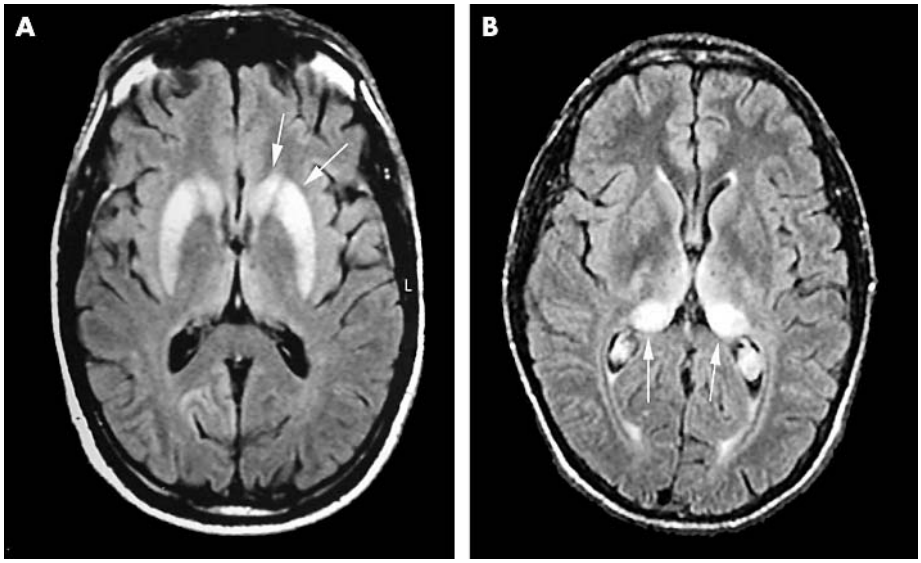

Figure 5 Magnetic resonance imaging in CJD. (A) sCJD: axial FLAIR image at the level of the basal ganglia showing symmetrical high signal in the caudate head and anterior putamen (arrows). (B) vCJD: axial FLAIR image at the level of the basal ganglia showing symmetrical high signal in the pulvinar and dorsomedial nuclei of the thalamus (arrows). Courtesy of David Summers, National CJD Surveillance Unit.

What are they like?

Genetic prion diseases are very rare and a detailed description of their varied clinical features is not appropriate for this review. Genetic CJD caused by a point mutation may have a clinical profile not dissimilar to that of sCJD, although with a lower mean age of onset and a longer mean duration. GSS, in its classical form, tends to present with a progressive cerebellar ataxia, although the definition of GSS has become a little confused and increasingly neuropathological in nature.

FFI presents with prominent sleep and autonomic disturbances.

A few important general points can be made:

- The clinical phenotype of genetic prion disease, including the age of onset and illness duration, is extremely variable arising partly (but not entirely) from the different causative mutations. The clinical picture may not be uniform within a given pedigree
- Many cases of genetic prion disease may be clinically indistinguishable from non-genetic forms
- A family history of genetic prion disease may not be present (for a variety of reasons)
- These diseases are of autosomal dominant inheritance
- Penetrance is typically high and age dependant, but variable. In the case of E220K, penetrance is reported to be 0.45 by the age of 60 years and 0.96 by 80+
- The current view is that the underlying mutations are directly causal, requiring no external factor for disease. However, the possibility that there are susceptibility factors determining response to some common (unidentified) environmental factor cannot be entirely dismissed.

How do I diagnose genetic prion disease?

The fact that a family history may not be present, combined with the clinical variability and the potential for mimicking sCJD, has one clear implication: genetic prion disease cannot be absolutely excluded unless specific genetic testing is undertaken. Table 5 presents an outline of the diagnosis. Essentially, one has to suspect a prion disease, obtain a careful family history, and to undertake genetic testing for a recognised PRNP mutation.

Table 5 Diagnosis of genetic prion disease

Awareness of possibility Awareness of clinical phenotypic variability Exclusion of other diagnoses	Diagnosis of a prion disease (clinically or neuropathologically)
Family history Blood test: PRNP mutation screening	

IATROGENIC CJD

What is iatrogenic CJD?

Over the past 30 years about 300 cases of CJD have been caused by the transmission of infection from person to person in the course of medical or surgical treatments. The first case was described in 1974 and involved the development of CJD 18 months after the insertion of a corneal graft obtained from a patient who themselves had died of CJD; shortly after this two cases linked to depth EEG electrodes were identified. In retrospect, transmission of CJD via neurosurgical instruments probably occurred in the 1950s in three cases operated on in the same theatre with instruments previously used in cases of CJD. In the 1980s iatrogenic transmission via human pituitary growth hormone and human dura mater grafts was recognised. Human pituitary hormones were produced from pools containing many thousands of cadaveric glands and the presumption is that pituitaries from patients with CJD were inadvertently included in the production process. Human dura mater grafts were also obtained from cadavers and the great majority of cases of CJD linked to this treatment were given a specific brand of dura, Lyodura. There may have been pooling of glands during production with the potential for cross contamination from a sample of dura mater obtained from a patient with CJD.

Variation at codon 129 of PRNP influences susceptibility to iatrogenic CJD. In cases related to infection in or adjacent to the brain—for example, dura mater grafts—codon 129MM is a risk factor, but with peripheral infection—for example, pituitary hormone treatment (which was administered by injection)—homozygosity, either MM or VV, is a risk factor.

What is iatrogenic CJD like?

The clinical presentation of iatrogenic CJD is determined by the route of exposure. In cases with effective inoculation into the central nervous system (CNS)—for example, via neurosurgical instruments—the clinical features are

indistinguishable from sporadic CJD, with rapidly progressive dementia and myoclonus. Survival is usually measured in months. With a peripheral route, such as human pituitary hormone treatment, there is initially a progressive cerebellar syndrome, usually affecting gait in particular, and other focal signs such as myoclonus only develop later in the clinical course. Cognitive impairment and/or dementia occur only rarely and in many cases meaningful communication is possible until the terminal stages. The mean survival is about a year. In cases related to human dura mater grafts there is heterogeneity, with many cases presenting with clinical features similar to sporadic CJD, although in some cases there is early ataxia and relatively prolonged survival.

The fact that the clinical presentation in iatrogenic CJD is influenced by the route of exposure is of scientific interest as kuru, the disease in Papua New Guinea linked to ritual cannibalism, is caused by a peripheral route of exposure and also presents with a predominant cerebellar syndrome. That direct CNS infection results in a clinical picture similar to sporadic CJD may be an argument in support of the hypothesis that sporadic CJD develops following the spontaneous generation of disease associated prion protein in the brain.

How do I diagnose iatrogenic CJD?

Cases of iatrogenic CJD may be missed without an awareness of the relevant risk factors, and obtaining a history of potentially relevant exposures is critical to raising the possibility of a diagnosis of iatrogenic CJD. In cases of suspect CJD and in patients with an unexplained progressive neurological disorder, specific enquiry should be made about previous neurosurgical or eye operations and about prior pituitary hormone treatment. In cases with a potential iatrogenic risk factor it is essential to carry out appropriate investigation as neurological deterioration may reflect a recurrence of the condition for which the original treatment was given rather than CJD. For example, human growth hormone treatment may have been given following resection of a primary brain tumour and recurrence may result in a clinical picture similar to iatrogenic CJD, particularly if the tumour is in the cerebellum.

Recommendations for the investigation of iatrogenic CJD are the same as for sporadic cases. The EEG may show periodic complexes in cases with central infection, but these appearances are rarely, if ever, found in pituitary hormone related CJD. There is limited information on the utility of CSF 14-3-3 assay in iatrogenic CJD, but there are preliminary data to suggest that this investigation can be helpful in all forms of iatrogenic CJD, including cases related to growth hormone treatment. There are also limited data on MRI scan, but high signal in the putamen and caudate have been found in a significant proportion of growth hormone related cases.

VARIANT CJD

What is variant CJD?

In 1996 10 cases of CJD were identified in the UK with novel clinical and pathological features, and it was hypothesised that this new variant of CJD (now called variant CJD) was caused by human infection with bovine spongiform encephalopathy (BSE). Subsequent research, including laboratory transmission studies in mice, has provided convincing evidence that variant CJD is indeed caused by the BSE agent; the failure to find cases of CJD with a similar phenotype in archives in the UK and other countries strongly supports the hypothesis that this is indeed a new disease. To date over 140 cases of variant CJD have been identified in the UK and a small number of cases have been found in other countries, including France, Ireland, Italy, the USA, and Canada. It is of note that, although some of these cases may have been exposed to BSE infection indigenously, the single cases in the USA and Canada had a history of residence in the UK in the 1980s when human exposure to BSE was most likely. The favoured hypothesis is that variant CJD is the result of infection through dietary exposure to BSE and probably to bovine CNS tissues, which contained high levels of infectivity in the 1980s. There was concern about the possibility of a major epidemic of variant CJD; although there remain many uncertainties, recent analyses suggest that the annual mortality rate in the UK may have peaked.

Table 6 Differences between sporadic and variant CJD

	sCJD	vCJD
Mean age at death	66 years	29 years
Median duration of illness	4 months	14 months
Thalamic MRI high signal	Caudate/putamen 60%	Pulvinar 90%
EEG	"Typical" 70%	"Typical" 0%
Neuropathology	Plaques 10%	Florid plaques 100%

All tested cases of variant CJD, to date, have been codon 129MM.

It is, however, possible that cases with an alternative codon 129 genotype may occur in the future as variations at this locus can influence incubation period. There is also the possibility that the clinical and pathological features in such cases might differ from variant CJD with an MM background.

What is variant CJD like?

Variant CJD affects young people, with a mean age at death of 29 years (range 15–73 years) in contrast to a mean age at death in sporadic CJD of 65 years (fig 2). The early clinical course is dominated by psychiatric symptoms, including depression, withdrawal, and anxiety, although a minority of cases have early neurological symptoms in the form of cognitive impairment and, notably, persistent painful sensory symptoms. After a mean of six months ataxia develops and this is associated with involuntary movements, which may be choreiform, dystonic, or myoclonic. There is progressive cognitive impairment and other focal signs may occur, including dysphasia, rigidity, hyperreflexia, and primitive reflexes. The later stages are similar to sporadic CJD, with terminal akinetic mutism in many cases. The mean survival is 14 months, but some patients have survived over three years from the first symptom (fig 3).

How do I diagnose variant CJD?

Early diagnosis of variant CJD may be impossible as the psychiatric features are indistinguishable from common psychiatric disorders. In a minority of cases the combination of psychiatric symptoms with painful sensory symptoms and/or cognitive problems may raise the suspicion of an underlying neurological disorder, but the possibility of a diagnosis of variant CJD usually depends on the evolution of neurological features and, in particular, the development of ataxia and involuntary movements. The combination of early

psychiatric symptoms followed by progressive cognitive and neurological deterioration should raise the possibility of the diagnosis of variant CJD. The EEG never shows periodic complexes in variant CJD and the CSF 14-3-3 assay is positive in only about 50% of cases. The MRI scan is the most helpful non-invasive investigation, showing high signal in the posterior thalamus, the ''pulvinar sign'', on T2 and especially FLAIR sequences in about 90% of cases (fig 5). Diagnostic criteria for variant CJD have been formulated (available on www.cjd.ed.ac.uk) and, to date, a diagnosis of ''probable'' variant CJD has had 100% specificity. Tonsil biopsy may allow the identification of the disease associated prion protein, but, like brain biopsy, is an invasive procedure with potential risks. Table 6 lists some important distinctions between variant and sporadic CJD.

WHAT SHOULD I DO?

The potential for iatrogenic transmission of sporadic CJD underlines the importance of human prion diseases for public health. The risks from variant CJD may be greater because the disease associated prion protein is found at higher levels in lymphoreticular tissues in this condition than in other human prion diseases, and a number of policies have been instituted to reduce the risk of onward transmission—for example, universal leucodepletion of blood donations. CJD is not a notifiable disease, but there is a need to follow guidelines to protect public health. The Department of Health has recently issued revised advice, which is available at http://www.doh.gov.uk/cjd/tseguidance. Of particular importance is the recommendation to inform the local consultant in communicable disease control of any suspect case of CJD and to inform the CJD Incidents Panel (CJD Incidents Panel, Health Protection Agency, CDSC, 61 Colindale Avenue, London NW9 5EQ; tel 0208 200 6868 ex8074, fax 0208 200 7868) of any case of CJD in which there is a risk that surgical instruments may have been contaminated and re-used.

There is no proven treatment for CJD. Press reports of a benefit from treatment with quinacrine and/or chlorpromazine have not been substantiated on the basis of anecdotal reports and a review by the French drug agency (available on http://www.sante.gouv.fr/htm/actu/sssp020408/7securite.htm). Following a High Court hearing pentosan polysulfate has been given to one patient by intraventricular infusion (this drug does not cross the blood–brain barrier), but the outcome is not yet known.

Since 1990 the Department of Health has funded the National CJD Surveillance Unit with a remit to study the clinical characteristics, neuropathology, and epidemiology of CJD. The national CSF 14-3-3 laboratory is situated within the unit. All cases of suspect CJD should be referred to:

- National CJD Surveillance Unit, Bryan Matthews Building, Western General Hospital, Crewe Road, Edinburgh EH4 2XU; tel 0131 537 2128, fax 0131 343 1404; r.knight@ed.ac.uk or r.g.will@ed.ac.uk.

A National Care Package for all forms of CJD is also based at the unit, with a remit to optimise the care of patients with CJD and their families. The contact details are:

- National Care Team, National CJD Surveillance Unit, Bryan Matthews Building, Western General Hospital, Crewe Road, Edinburgh EH4 2XU; tel 0131 537 3073; fax 0131 343 1404; susan.macdonald@ed.ac.uk

Support for patients and their families is also available from the following organisations:

- Mrs Gillian Turner, CJD Support Network, PO Box 346, Market Drayton, Shropshire, TF9 4WN; tel 01630 673 993 Helpline; info@cjdsupport.net
- Mrs Frances Hall, Human BSE Foundation Helpline, 99 Warkworth Avenue, Chester Le Street, County Durham, DH2 3TW; tel 0191 389 4157/4004; fax 0191 389 4004; hbsef@btinternet.com

The Prion Research Group at the National Hospital, Queen Square and the Prion Clinic at St Mary's Hospital have a longstanding interest in research in many aspects of human prion disease, including basic scientific research, genetic disease, and treatment trials. Contact details are:

- Dr Angus Kennedy, National Prion Clinic, Department of Neurology, St Mary's Hospital, Praed Street, London W2 1NY; tel (0207) 886 7775 or 6883; fax (0207) 886 3746; help.prion@st-marys.nhs.uk
- Professor J Collinge, MRC Prion Unit, Department of Neurodegenerative Diseases, National Hospital for Neurology & Neurosurgery, Queen Square, London WC1N 3BG; tel (0207) 837 3611 National Hospital; fax (0207) 837 8047; j.collinge@prion.ucl.ac.uk

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5 **Will RG**, Alpers MP, Dormont D, *et al*. Infectious and sporadic prion diseases. In: Prusiner SB, e, eds. *Prion biology and diseases*. New York: Cold Spring Harbour Laboratory Press, 1999:465–507.
- **A review of the clinical, epidemiological, and other features of sporadic, variant, and iatrogenic CJD with a comprehensive reference list.**